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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,945	08/23/2005	Andrea Capocchi	263361US0PCT	4907
22850 7590 11/20/2007 OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			EXAMINER HENRY, MICHAEL C	
			ART UNIT 1623	PAPER NUMBER
			NOTIFICATION DATE 11/20/2007	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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# Office Action Summary

Application No.

10/516,945

Applicant(s)

CAPOCCHI, ANDREA

Examiner

Michael C. Henry

Art Unit

1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 16 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 24-36 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 24-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The following office action is a responsive to the Amendment filed, 08/16/07.

The amendment filed 08/16/07 affects the application, 10/516,945 as follows:

1. Claims 11-23 have been canceled. New Claims 24-36 have been added.
2. The responsive to applicants' declaration, amendments and arguments is contained herein below.

Claims 24-36 are pending in application

#### ***Claim Objections***

Claim 24 is objected to because of the following informalities: Claim 24 contains two periods. However, each claim should begin with a capital letter and end with a period. Periods may not be used elsewhere in the claims except for abbreviations. See *Fressola v. Manbeck*, 36 USPQ2d 1211 (D.D.C. 1995). Appropriate correction is required.

Claim 24 is objected to because of the following informalities: The claim has two consecutive steps that are both labeled as "c)". This appears to be typographical error. Appropriate correction is required.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 24-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiesi et al. (EP 0153998 A2).

In claim 24, applicant claims a process of lyophilization for the preparation of a piroxicam: $\beta$ -cyclodextrin inclusion compound in a 1:2.5 molar ratio comprising: a) dissolving piroxicam and  $\beta$ -cyclodextrin in the molar ratio of 1 to 2.5 and ammonium hydroxide in water brought to a temperature of at least 60 °C; b) bringing the resulting solution to the temperature of -10 °C of complete freezing; c) further lowering the temperature of the frozen solution to at least -20 °C; and c) drying the frozen solution under vacuum. wherein the temperature of -10 °C of complete freezing of the hot solution of step a) is achieved at a cooling rate equal to or higher than 1 °C/min. Dependent claims 24-28 and 31-33 are drawn to the use of specific temperatures and cooling rates. Claims 29 and 30 are drawn to said method wherein the hot solution is specifically cooled and poured in liquid nitrogen and wherein the product is obtained in specific form. Claim 34 is drawn said method involving the use of specific % concentration and weight ratio of ammonium hydroxide to the piroxicam. Claims 35 and 36 are drawn to said method with specific time of achieving the temperature of freezing the hot solution, and wherein the process is conducted on an industrial scale.

Chiesi et al. disclose a process of lyophilization for the preparation of a piroxicam; $\beta$ -cyclodextrin inclusion compound in a 1:2.5 molar ratio (0.088:0.220 moles) comprising dissolving piroxicam and  $\beta$ -cyclodextrin in the molar ratio of 1 to 2.5 and 30% ammonium hydroxide in water brought to a temperature of 60 °C; bringing the hot solution to the temperature of -20 °C of complete freezing and drying the frozen solution under vacuum (freeze drying) (see pages 3-4, example 4). It should also be noted that applicant further claims a lowering of temperature of their solution to a temperature -20 °C which is the same temperature to which Chiesi et al. lowers their solution (see applicant's, claim 24).

The difference between applicant's claimed method and the method of Chiesi et al. is that applicant freezes or cools their solution to a temperature of -10 °C then further to -20 °C whereas Chiesi et al.'s freezes or cools their solution to a temperature of -20 °C, and Chiesi et al.'s is silent about the rate of cooling or freezing rate of said solution. However, Chiesi et al.'s disclose that their solution can be freeze dried in general and thus a skilled artisan would be motivated to adjust the physical parameters used in Chiesi et al.'s method such as temperature so as to optimize the reaction conditions and/or based on factors such as availability or need. Also, even if the rate of cooling or freezing was different, the rate of cooling or freezing should not affect the product formed especially since applicant's claimed lyophilized product is the same as Chiesi et al.'s lyophilized product and since they both used the same reactants to produce their said lyophilized product.

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made to have used the process of Chiesi et al., and to make adjustments to condition parameters like the temperature and the rate of cooling or freezing in order to prepare Chiesi et al.'s composition, to treat arthro-rheumatic diseases.

One having ordinary skill in the art would have been motivated, to use the process of Chiesi et al., and to make adjustments to condition parameters like the temperature and the rate of cooling or freezing in order to prepare Chiesi et al.'s composition, to treat arthro-rheumatic diseases, because a skilled artisan would reasonably be expected to adjust said parameters so as to optimize the reaction conditions and/or based on factors such as availability or need. It should be noted that a skilled artisan would be motivated to adjust the physical parameters used in

Art Unit: 1623

Chiesi et al.'s method such as temperature, the manner of cooling and rate of cooling the solution so as to optimize the reaction conditions and/or based on factors such as availability or need.

***Response to Arguments***

Applicant's arguments with respect to claim 24-36 have been considered but are not found convincing.

The Declaration under 37 CFR 1.132 filed 05/03/07 is insufficient to overcome the rejection of claims 24-36 based upon Chiesi et al. (EP 0153998 A2) as set forth in the last Office action because: Applicant's declaration pertains to demonstrating that pre-cooling the shelves of the freeze-dryer to a temperature of -20° C is not sufficient for achieving a cooling rate equal to or higher than 1° C/min, and hence for obtaining a product characterized by: i) completeness of the inclusion reaction; and ii) complete amorphization, and wherein piroxicam is present in the zwitter-ionic form. The declaration fails to set forth any convincing reason or evidence that indicates their claimed process produces a product that is not the same or that is different from the product of the applied prior art document. For example, the declaration discloses that the under the conditions of cooling for Chiesi et al.'s process, "it has been observed that, when the solution reaches the temperature of 50-55°C,  $\beta$ -cyclodextrin begins to re-crystallize causing de-complexation of piroxicam. However, whatever happens to the solution at a temperature of 50-55°C is irrelevant, is not claimed, and does not alter the fact that Chiesi et al.'s process produces a complex of piroxicam: $\beta$ -cyclodextrin complex of the same molar ratio (1:2.5) of piroxicam to  $\beta$ -cyclodextrin at the same claimed temperature of -20°C, as claimed by applicant. It should be noted that applicant has not presented any facts or evidence which describes Chiesi et al.'s final product (i.e., the piroxicam: $\beta$ -cyclodextrin complex) much less comparative scientific (such as

Art Unit: 1623

chemical and physical) data that characterizes Chiesi et al.'s final product as compared to applicant's product. Moreover, applicant's has not demonstrated that their method produces a different product from Chiesi et al.'s product. The declaration discloses that by applying said temperature to the shelves, the solution reaches the freezing temperature of  $-10^{\circ}\text{C}$  in 120 min, and hence at a cooling rate of about  $0.7^{\circ}\text{C}/\text{min}$ , so lower than  $1^{\circ}\text{C}/\text{min}$ . However, the declaration does not disclose whether or not Chiesi et al.'s product is the same as applicant's at  $-10^{\circ}\text{C}$ , especially in terms of being of "complete freezing". Also, one of ordinary skill in the art would expect that by applying a temperature of  $-20^{\circ}\text{C}$  to the shelves that Chiesi et al.'s product or process would reach a temperature of  $-20^{\circ}\text{C}$  due to temperature equilibration of the reaction, lyophilization process or system. In fact, based on their teaching one of ordinary skill in the art would deduce that Chiesi et al. applied a temperature of  $-20^{\circ}\text{C}$  to the shelves so until the process reached or equilibrated to and occurred to completion at said temperature of  $-20^{\circ}\text{C}$  (which is a temperature below the eutectic temperature of  $-18^{\circ}\text{C}$  wherein lyophilization occurs). The declaration discloses that applicant's product is characterized by: i) completeness of the inclusion reaction; and ii) complete amorphization, and wherein piroxicam is present in the zwitter-ionic form. However, although these physical characteristics are not claimed by applicant, applicant has not demonstrated that Chiesi et al.'s product does not have the same said characteristics. Moreover, applicant's has not demonstrated that their method produces a different product from Chiesi et al.'s product, nor is their claimed method patentable over Chiesi et al.

The applicant argues that this well-defined and controlled cooling rate allows one to obtain a piroxicam: $\beta$ -cyclodextrin complex characterized by complete inclusion and complete amorphization, where the piroxicam is present in the zwitterionic form. However, applicant has

Art Unit: 1623

not shown or demonstrated that Chiesi et al.'s piroxicam: $\beta$ -cyclodextrin complex is not characterized by complete inclusion and complete amorphization, where the piroxicam is present in the zwitterionic form. Furthermore, Chiesi et al. disclose the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam: $\beta$ -cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam: $\beta$ -cyclodextrin complex like applicant's is characterized by complete inclusion. Also, Chiesi et al.'s piroxicam: $\beta$ -cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to  $\beta$ -cyclodextrin which implies that Chiesi et al.'s piroxicam: $\beta$ -cyclodextrin inclusion complex should also be characterized as having complete inclusion. It should be noted that both applicant's and Chiesi et al.'s lyophilized product is the same piroxicam: $\beta$ -cyclodextrin complex that are prepared by use of the same reactants. In addition, it should be noted that the applicant in example 1 (on page 10, line 16 to page 11, line 1 of the specification) disclose that "a solution was poured through the tap on the temperature-controlled shelves of the freeze-dryer pre-cooled at -40°C. After 210 min, the frozen product reaches the temperature of -30°C." For, this process the cooling rate is less than that disclosed by applicant in the applicant's declaration presented to demonstrate Chiesi et al.'s cooling rate for the preparation of said complex. However, applicant's piroxicam: $\beta$ -cyclodextrin complex at the lower cooling rate still produces amorphous products (see page 11, line 1 of the specification). Thus, Chiesi et al.'s higher cooling rate should also produce an amorphous product. It should be noted that applicant does not claim an amorphous or amorphized product, nor a product wherein piroxicam is present in the zwitterionic form. Also, it should be noted that applicant has not presented any facts or evidence which describes Chiesi et al.'s product much less compares Chiesi et al.'s product to applicant's



Art Unit: 1623

product. Moreover, applicant's has not demonstrated that their method produces a different product from Chiesi et al.'s product.

The applicant argues that under the conditions of cooling for Chiesi et al.'s process, "it has been observed that, when the solution reaches the temperature of 50-55°C,  $\beta$ -cyclodextrin begins to re-crystallize causing de-complexation of piroxicam. However, whatever happens to the solution at a temperature of 50-55°C is irrelevant, is not claimed, and does not alter the fact that Chiesi et al.'s process produces a complex of piroxicam: $\beta$ -cyclodextrin complex of the same molar ratio (1:2.5) of piroxicam to  $\beta$ -cyclodextrin at the same claimed temperature of -20°C, as claimed by applicant.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

### ***Conclusion***

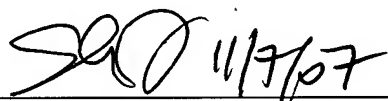
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652.

Art Unit: 1623

The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael C. Henry

  
\_\_\_\_\_  
Shaojia Anna Jiang, Ph.D.  
Supervisory Patent Examiner  
Art Unit 1623

November 6, 2007.